Carvedilol prevents cardiac hypertrophy and overexpression of hypoxia-inducible factor-1alpha and vascular endothelial growth factor in pressure-overloaded rat heart

徐國基

Shyu KG;Liou JY;Wang BW;Fang WJ;Chang H

摘要

Abstract

The use of beta-blockers has emerged as a beneficial treatment for cardiac hypertrophy. Hypoxia-inducible factor-1alpha (HIF-1alpha) is tightly regulated in the ventricular myocardium. However, the expression of HIF-1alpha in cardiac hypertrophy due to pressure overload and after treatment with beta-blocker is little known. To evaluate the effect of carvedilol on both myocardial HIF-1alpha expression and cardiac hypertrophy, infra-renal aortic banding was performed for 4 weeks in adult Sprague-Dawley rats to induce cardiac hypertrophy. Carvedilol at 50 mg/kg body weight per day after surgery was given. Heart weight and the ratio of heart weight and body weight increased significantly after aortic banding for 4 weeks in the absence of drug treatment. Mean arterial pressure increased from 80 +/- 9 mmHg in the sham group to 94 +/-5 mmHg ($p < 0.001$) in the banding group. Echocardiography showed concentric hypertrophy after aortic banding. Mean arterial pressure decreased after treatment with carvedilol. The increased wall thickness and heart weight was reversed to normal by carvedilol. Western blot showed that HIF-1alpha, vascular endothelial growth factor (VEGF) and brain natriuretic peptide (BNP) proteins were up-regulated and nerve growth factor-beta (NGF-beta) down-regulated in the banding group. Treatment with valsartan, doxazosin, or N-acetylcysteine did not significantly affect HIF-1alpha and VEGF proteins expression in the banding groups. Real-time polymerase chain reaction showed that mRNA of HIF-1alpha, VEGF and BNP increased and

mRNA of NGF-beta decreased in the banding group. Treatment with carvedilol reversed both protein and mRNA of HIF-1alpha, VEGF, BNP, and NGF-beta to the baseline values. Increased immunohistochemical labeling of HIF-1alpha, VEGF, and BNP in the ventricular myocardium was observed in the banding group and carvedilol again normalized the labeling. In conclusion, HIF-1alpha, VEGF, and BNP mRNA and protein expression were up-regulated, while NGF-beta mRNA and protein was downregulated in the rat model of pressure-overloaded cardiac hypertrophy. Treatment with carvedilol is associated with a reversal of abnormal regulation of HIF-1alpha, VEGF, BNP, and NGF-beta in the hypertrophic myocardium.